

## Heart Rate Variability in Patients With Ventricular Arrhythmias: Effect of Antiarrhythmic Drugs

GIULIO ZUANETTI, MD, ROBERTO LATINI, MD, JAMES M. M. NEILSON, PhD,\*  
PETER J. SCHWARTZ, MD, FACC, DAVID J. EWING, MD\* AND THE ANTIARRHYTHMIC DRUG  
EVALUATION GROUP (ADEG)†

Milan, Italy and Edinburgh, Scotland

The purpose of this study was to investigate whether heart rate variability could be reliably assessed in patients with ventricular arrhythmias and to evaluate whether it is affected by antiarrhythmic drugs. The study was based on an analysis of 239 ambulatory electrocardiographic (ECG) recordings obtained from 67 patients with frequent and complex ventricular arrhythmias enrolled in the Antiarrhythmic Drug Evaluation Group (ADEG) study. In each recording, after exclusion of premature ventricular complexes, the number of times during a 24 h period in which two consecutive sinus RR intervals differed by more than 50 ms was calculated. The total 24 h count from each recording was then used as an index of heart rate variability. This method is a reliable marker of cardiac parasympathetic activity.

Recordings were analyzed at baseline ( $n = 56$ ), during long-term treatment with amiodarone ( $n = 17$ ), flecainide ( $n = 22$ ) or propafenone ( $n = 17$ ) and after washout in selected patients ( $n = 5$ ). Despite the presence of a different number of arrhythmias, total 24 h counts in the same patient appeared reproducible over time ( $r = 0.83$  between two different recordings,  $n = 49$ ,  $p < 0.0001$ ).

In the last few years, several experimental (1-4) and clinical (5,6) studies have shown that signs of reduced vagal activity are associated with an enhanced risk of sudden cardiac death. Frequent and complex ventricular arrhythmias also constitute an independent risk factor for sudden cardiac death (7,8), and prevention or reduction of arrhythmias might be associated with reduced risk (9,10). However, some potent antiarrhythmic drugs may actually increase the incidence of death as demonstrated by the Cardiac Arrhythmia Suppression Trial (CAST) (11). The assessment of heart rate variability and autonomic control in patients with ar-

Baseline counts (median 1,698, range 26 to 13,648) were not correlated ( $r = 0.15$ ) with the number of arrhythmias. The three antiarrhythmic drugs had a disparate effect on total 24 h counts: no change was observed in patients treated with amiodarone (median percent change [ $\Delta\%$ ]-8,  $p = \text{NS}$ ), whereas a significant ( $p < 0.025$ ) decrease occurred in patients treated with flecainide (median  $\Delta\% -56\%$ ) or propafenone (median  $\Delta\% -64\%$ ). This effect was reversible after treatment was discontinued and was not related to suppression of arrhythmias because total 24 h counts were similar during treatment in the presence and absence of frequent arrhythmias.

These results indicate that heart rate variability can reliably be assessed by this total 24 h counts method in patients with frequent ventricular arrhythmias. The presence or suppression of arrhythmias itself did not modify heart rate variability. Class IC antiarrhythmic drugs may significantly affect heart rate variability, and this influence may contribute to the overall effect of these agents on mortality.

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rhythmia may identify those at greater risk and increase the understanding of the detrimental effect of some agents. However, to date, this analysis has been limited by technical problems. In this study, using 24 h ambulatory electrocardiographic recordings of heart rate (12), we adopted a time domain approach that appears to provide a sensitive and reliable index of cardiac vagal activity (12,13).

The purpose of this study was threefold. We investigated whether 1) this index of heart rate variability is reliable and reproducible in patients with frequent ventricular arrhythmia; 2) the suppression of arrhythmia affects heart rate variability; and 3) antiarrhythmic drugs with different effects on cardiac electrophysiology and contractility (14-16) modify heart rate variability independently of their antiarrhythmic action. The results have been presented in preliminary form elsewhere (17).

### Methods

We analyzed 24 h ambulatory electrocardiographic (ECG) recordings previously obtained from patients enrolled

From the Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy and the \*University Departments of Medicine, and Medical Physics and Medical Engineering, Royal Infirmary, Edinburgh, Scotland. †Centers participating in the study are listed in the Appendix. This study was supported in part by a grant from NATO Scientific Affairs Division, Brussels, Belgium, Dr. D. J. Ewing is a Wellcome Trust Senior Lecturer.

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Address for reprints: Giulio Zuanetti, MD, Istituto di Ricerche Farmacologiche Mario Negri, Via Eritrea, 62, 20157 Milan, Italy.

in the multicenter Antiarrhythmic Drug Evaluation Group (ADEG) study (18) at baseline, during long-term antiarrhythmic treatment and, in selected patients, after washout. The centers participating in the study are listed in the Appendix.

**Protocol of the ADEG Study.** The study group consisted of patients with cardiac disease: stabilized ischemic heart disease (severe stable angina documented by ECG and successfully treated by antianginal drugs excluding verapamil and diltiazem or myocardial infarction >8 weeks previously), dilated cardiomyopathy or hypertrophic cardiomyopathy in patients who presented with at least one of the following arrhythmias during 24 h ambulatory ECG recording: 1) sustained (>30 s) or nonsustained ventricular tachycardia defined as 4 or more consecutive ventricular ectopic beats at a rate >100 beats/min; 2) runs of  $\geq 3$  consecutive ventricular ectopic beats; 3) presence of polymorphic ectopic couplets; or 4) presence of monomorphic couplets with an RR interval <400 ms.

*Criteria for exclusion were:* second or third degree atrioventricular (AV) block; sick sinus syndrome (assessed by the attending physician from the 12 lead ECG or baseline 24 h ECG); thyroid dysfunction; hepatic or renal failure; concomitant treatment with a beta-adrenergic blocker, verapamil or diltiazem and a history of unsuccessful treatment with one of the three drugs under study.

*Eligible patients ( $n = 141$ ) were randomized to receive sequences of three antiarrhythmic agents:* amiodarone, flecainide and propafenone. Long-term treatment with amiodarone was started with a loading dosage of 600 to 800 mg/day for 7 days, followed by 200 mg/day, and with fixed doses of 200 mg/day for flecainide and 450 mg/day for propafenone.

*Response to antiarrhythmic treatment* was considered satisfactory if the recording during treatment revealed 1) suppression of sustained and nonsustained ventricular tachycardia, 2) reduction >90% of runs of three or four ventricular ectopic beats, and 3) >75% reduction of couplets. Reduction in the number of premature ventricular complexes was not used as a criterion for response.

*If the response was not satisfactory,* the drug dose was increased to 400 mg/day for amiodarone, 300 mg/day for flecainide and 900 mg/day for propafenone. If a patient did not respond to the drug or if severe adverse effects occurred at either dose, treatment with one of the other two drugs was substituted and the follow-up assessment was restarted. If the patients did not respond to the second drug, treatment with the third one was begun. Each patient was followed up for  $\geq 2$  years, with periodic examinations at 1 week and 1, 3, 6, 12, 18, 24 and 36 months of treatment. At each control visit, a 24 h ambulatory ECG was recorded, a blood sample was taken for estimating plasma concentration of the drug by high performance liquid chromatography (19-21) and an echocardiogram was performed. Although most of the participating centers had bidimensional echocardiographs, only M-mode shortening fraction was measured as an index of myocardial performance because at the start of patient

enrollment (in 1985), a few centers had only a monodimensional echocardiograph.

**Measurement of heart rate variability.** The tapes sent from each of the participating centers for quality control of arrhythmia counts were randomly selected and used for analysis of heart rate variability. Reel to reel tapes that could not be replayed directly on our equipment were copied onto cassette format before analysis. All tapes were then replayed through a Pathfinder arrhythmia analyzer (Reynolds Medical) at 120 times the original recording speed. Using the time reference track recorded on each tape, the replay speed was controlled to within 0.5%. Throughout the analysis, the signal was closely monitored by the operator using the Pathfinder ECG display to exclude tapes with nonsinus rhythms such as atrial fibrillation.

*The trigger section of the analyzer detects individual QRS waves in the ECG signal,* distinguishing them from P and T waves and muscle noise and artifacts accompanying the ECG, using a continuously adaptive threshold derived from the noise components by independent filtering. The accuracy with which each QRS wave can be detected depends on the quality of the recorded ECG, but it has been shown (22) that with tapes of routine quality false positive and false negative errors of detection can be restricted to approximately 12 per 24 h. Excessive noise, such as would cause QRS waves to be missed, automatically inhibits analysis until the noise subsides, at which time analysis is resumed. The Pathfinder detects QRS waves on shapes significantly different from the subject's normal QRS complex by comparison with a continuously updated example of this normal complex held in the analyzer memory. Such abnormal complexes are indicated as ventricular ectopic beats (23). To monitor more gradual alterations in QRS configuration (for example, during postural changes), the analyzer provides another threshold that defines how well a QRS wave must match the prevailing normal shape to qualify for use in the process of updating the normal model. During RR interval analysis, this threshold is set low so that only complexes with QRS shapes particularly well matched to that of the sinus beat are accepted as normal.

For each ECG complex in the recording, the Pathfinder generates an external pulse to signify the detection of a beat. If that QRS complex has been identified as of normal (sinus) configuration, another pulse is then generated. The pulses are passed to a BBC microcomputer programmed for the actual RR variability analysis. The assembly language program times the arrival of each beat and stores the result with 0.12 ms (real time) resolution. Subtracting the times between successive normal beats allows the calculation of normal-normal intervals, and subtraction of each interval from its predecessor allows the change in interval to be determined. Each change in interval is then compared with 50 ms. If an increase or decrease >50 ms has occurred, a positive or negative count is added to the total being accumulated for that hour (12). However, because we previously found no significant differences between positive and negative counts

(12), the results reported here refer to positive counts (that is, increases  $>50$  ms).

The program also continuously maintains time thresholds corresponding to 63% and 175% of the prevailing normal RR interval, and beats with intervals outside these limits are regarded as premature or pause (a possible missed trigger). Although this may lead to the exclusion of some sinus intervals, our previous experience indicates that excluding such intervals has minimal effects on the sensitivity of the test but substantially improves its specificity. Such significantly mistimed beats, together with all those indicated by the Pathfinder as not normal in shape, are rejected from consideration and the interval calculations are restarted from the next normal QRS complex.

The intervals thus excluded, together with all periods during which the analyzer was inhibited, are accumulated and used to calculate the percent of the record actually analyzed. Because not all the recordings were of the same duration, the total count in each recording was normalized to the equivalent for a complete 24 h record (100% analyzed) to facilitate comparisons. We excluded records of  $<18$  h duration and those in which  $<40\%$  was analyzable. The results are therefore presented as total 24 h count for each recording.

**Data analysis.** Different sets of recordings were used for the different purposes of the study. To assess the reproducibility of heart rate variability, we compared the counts in two recordings obtained in the same patient at least 8 days apart under similar clinical conditions ( $n = 49$ ). This included comparison between recordings at baseline and after drug washout ( $n = 5$ ), when the number of arrhythmias had returned to values similar to those at baseline study and between ambulatory ECG recordings obtained during drug treatment with a similar number of ventricular arrhythmias in the two recordings and similar plasma concentrations of the antiarrhythmic agents ( $n = 44$ ). Such comparisons allowed us to assess the role of the presence of frequent ventricular arrhythmias as a possible confounding factor for the reproducibility of the recordings in these patients.

*The effect of the three drugs on heart rate variability was assessed by determining the changes in the number of counts during maintenance treatment (a minimum of 8 days for flecainide and propafenone and 21 days for amiodarone) compared with baseline values. Because of the nonnormal distribution of the data which became normal after logarithmic transformation, statistical analysis was performed with use of nonparametric tests on the original data (Kruskal-Wallis test for group comparisons and Wilcoxon rank test for analysis of changes within the same patient) and a parametric test (paired  $t$  test) after logarithmic transformation. Correlation between two variables was also performed on the transformed data by using the Pearson R coefficient. The chi-square statistic with Yates' correction when needed was used to compare incidence of events.*

## Results

**Study patients.** A total of 285 ECG tapes from 76 patients were used for the analysis of heart rate variability. Of these tapes, 66 were recorded at baseline, 211 at different times during treatment with the first drug of the sequence and 8 after drug washout. Forty-eight (16.7%) of the recordings were excluded from the analysis for technical reasons. This group included 24 tapes with unacceptable noise and repetitive shifts in the amplitude or configuration of the sinus QRS complex, nonsinus rhythms or excessively large P and T waves that made triggering erratic and unpredictable; 10 tapes with a duration  $<18$  h; 6 tapes from patients with bundle branch block in which consistent recognition of the premature ventricular beats was not possible and 8 tapes in which the presence of very frequent arrhythmias meant that  $<40\%$  of the tape was analyzable (usually between 30,000 and 40,000 premature ventricular complexes in the 24 h recording period), making a meaningful assessment of heart rate variability impossible.

Characteristics of the 67 patients for which data on heart rate variability were obtained from one or more ambulatory ECG recording are summarized in Table 1. These patients did not differ from the remaining group of patients in the Antiarrhythmic Drug Evaluation Group (ADEG) study, whose characteristics are also shown in Table 1. The mean percent duration of each individual recording available for baseline analysis was 83% (range 44% to 99%) and increased significantly ( $p < 0.01$ ) to 90% (range 45% to 99%) because of a lower number of arrhythmias for recordings during drug treatment.

**Baseline heart rate variability.** Fifty-six ambulatory ECG recordings were amenable to analysis of baseline heart rate variability before antiarrhythmic drug treatment. The median number of total 24 h counts was 1,698 (range 26 to 13,648), whereas the median number of arrhythmias in the same patients was 3,306 (range 110 to 39,587). Median values and range of counts were not significantly different for the different cardiac disorders or when different concomitant pharmacologic treatments (for example, digitalis or diuretic drugs) were taken into account. Counts and number of arrhythmias at baseline ( $n = 56$ ) are plotted on a logarithmic scale in Figure 1. There was no significant correlation ( $r = 0.15$ ,  $p = \text{NS}$ ) between these two variables. The nine diabetic patients did not have significantly different total 24 h counts from those of other patients.

**Reproducibility of the recordings.** In the 49 patients in whom the long-term reproducibility of heart rate variability was assessed (in 44 during drug treatment and in 5 without treatment), the median interval between recordings was 192 days (range 8 to 910). Total 24 h counts in the first and second recording in the same patient are plotted on a logarithmic scale in Figure 2. There was a high correlation between the two recordings ( $r = 0.83$ ) and a limited scatter of values around the line of identity. Because a high correlation coefficient does not necessarily imply good agreement be-

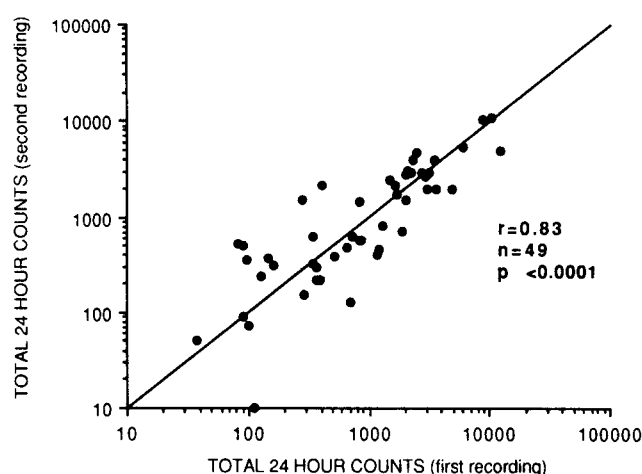
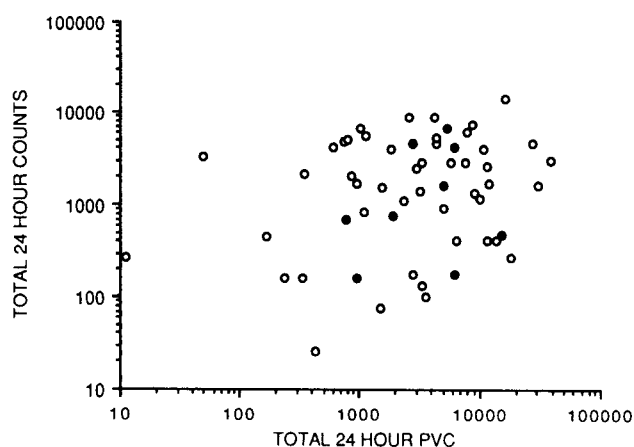
**Table 1.** Characteristics of 141 Patients in the Antiarrhythmic Drug Evaluation Group (ADEG) Study With and Without Assessment of Heart Rate Variability (HRV)

	HRV Assessed (n = 67)	HVR Not Assessed (n = 74)
Age (yr)*	59 ± 8 (36-83)	58 ± 9 (37-84)
Male/female	62/5	68/6
Diagnosis		
Ischemic heart disease	50 (74%)	53 (72%)
Dilated cardiomyopathy	15 (23%)	20 (27%)
Hypertrophic cardiomyopathy	2 (3%)	1 (1%)
Total PVCs/24 h†	3,890 (11-39,587)	3,047 (15-39,637)
Couplets/24 h†	56 (0-3,870)	40 (0-2,251)
Runs of nonsustained VT/24 h†	2 (0-999)	2 (0-358)
NYHA functional class		
I	35 (53%)	38 (51%)
II	27 (40%)	31 (42%)
III	5 (7%)	5 (7%)
Shortening fraction (%)*	24 ± 9	19 ± 7
Diabetes	9 (14%)	11 (15%)
Concomitant therapy		
Digitalis	25 (37%)	29 (39%)
Diuretics	34 (51%)	35 (48%)
Other	31 (46%)	35 (48%)

\*Mean ± SD (range); †median (range). NYHA = New York Heart Association; PVCs = premature ventricular complexes; VT = ventricular tachycardia.

tween two recordings (24), we further quantified the reproducibility of our data by calculating a coefficient of repeatability, according to the method of Bland and Altman (25),

**Figure 1.** Number of premature ventricular complexes (PVC) versus total 24 h counts in baseline recordings from 56 patients with ventricular arrhythmias. Diabetic patients are indicated by closed circles. No correlation is demonstrated between the two variables.

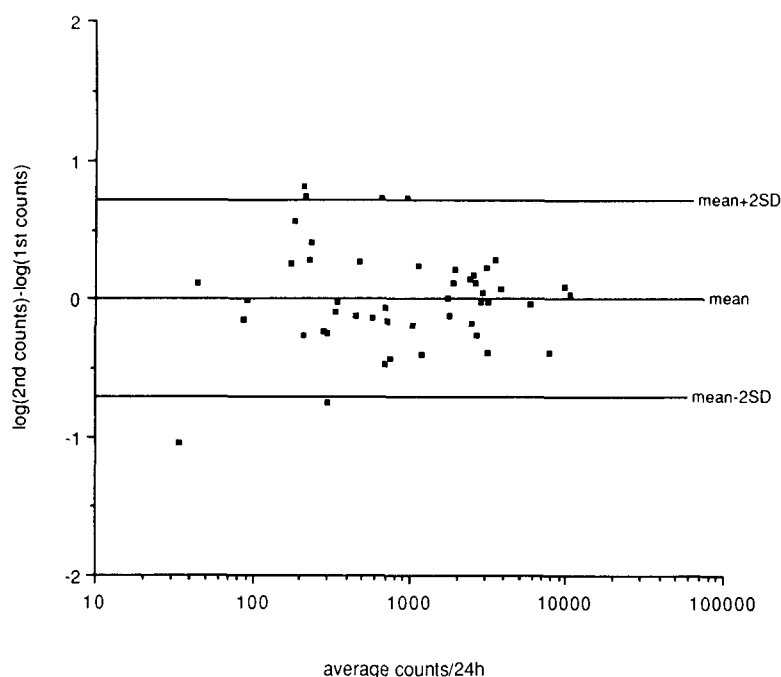


**Figure 2.** Individual total 24 h counts on the first (x axis) and the second occasion (y axis) in 49 patients with ventricular arrhythmias. The line of identity between the two recordings is indicated.

after logarithmic transformation of the data (Fig. 3). The mean of the differences (d) between the 49 pairs of recordings was very close to zero ( $d = 0.03$ ), thus allowing assessment of repeatability. The coefficient of repeatability, calculated for all patients, was 0.72; when one outlier of this limit was excluded, it was 0.66. This value corresponds to a 376% increase in counts and to a 76% decrease in counts. These values may be considered as limits for a biologically important change in heart rate variability. These results indicate that our index of heart rate variability, using total 24 h counts, is reproducible in patients with large numbers of ectopic beats and can reliably be used to assess the effect of pharmacologic treatment of heart rate variability.

**Effect of antiarrhythmic drugs on heart rate variability (Table 2).** In 56 patients, ambulatory ECGs obtained at baseline and during maintenance treatment with one of the three drugs were amenable to analysis. Total counts at baseline study were slightly lower for patients subsequently treated with amiodarone, but these differences were not significant (Kruskal-Wallis test). The three drugs had a disparate effect: amiodarone did not modify total 24 h counts significantly, whereas both flecainide and propafenone did. The median percent change of counts was -8% for amiodarone ( $p = \text{NS}$  versus baseline); -56% for flecainide ( $p = 0.005$  versus baseline, Wilcoxon signed rank test and  $p = 0.036$  paired  $t$  test); and -64% for propafenone ( $p = 0.022$  versus baseline, Wilcoxon signed rank test, and  $p = 0.0085$  paired  $t$  test). This disparate effect is illustrated in Figure 4, in which changes in the number of counts from baseline are shown for all three drugs.

A major (>76%) reduction in the number of counts occurred in 6% of patients treated with amiodarone (similar to the overall reproducibility data), 22% treated with flecainide ( $p < 0.05$  versus the overall reproducibility data) and 35% treated with propafenone ( $p < 0.05$  versus the overall reproducibility data). This effect of antiarrhythmic drugs on total 24 h counts was not related to changes in mean



**Figure 3.** Plot of difference between second and first counts (y axis) and average count in the 49 patients. The central horizontal line indicates the mean difference, whereas the upper and lower horizontal lines correspond to mean  $\pm 2$  standard deviation (SD). Note that the mean difference is very close to zero, indicating the absence of any bias in the analysis. More than 95% of the differences lie between the  $\pm 2$  standard deviation limits. The lowest point is the outlier excluded from the calculation of the coefficient of repeatability.

heart rate, which was decreased during amiodarone treatment ( $p < 0.001$ ), but remained unchanged during treatment with flecainide and propafenone (Table 2). M-mode echocardiography performed at baseline study and during treatment revealed no significant changes in shortening fraction. No relation was found between type of cardiac disease and drug effect on total 24 h counts.

At the time of recording during treatment, the median plasma drug concentration in patients treated with amiodarone was 720 ng/ml (range 156 to 9,990) for the parent compound and 640 ng/ml (range 167 to 7,067) for its active metabolite desethylamiodarone. For patients treated with flecainide, it was 375 ng/ml (range 54 to 1,199) and for patients treated with propafenone, it was 245 ng/ml (range 10 to 6,303) for the parent compound and 98 ng/ml (range 10 to 6,984) for its active metabolite 5-OH-propafenone. No correlation was found between plasma concentration of the drug and its effect on total 24 h counts.

To ascertain further that the changes observed were not related to a spontaneous decrease in heart rate variability

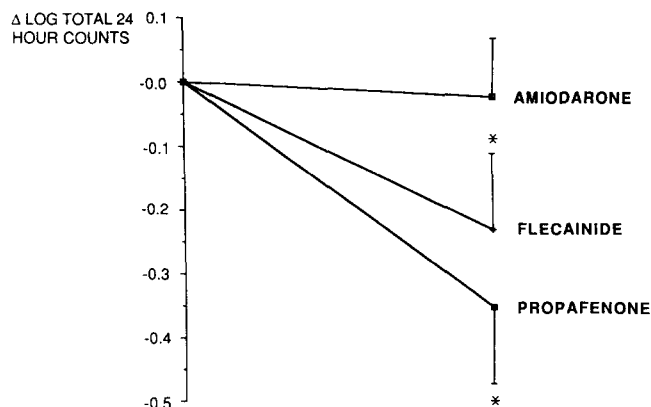
due to the progression of cardiac disease but were a result of the effect of the drug, ambulatory ECGs from five patients (four treated with flecainide and one treated with propafenone) were analyzed after washout (Fig. 5). The effect was reversible in four (80%) of the five patients. Although the number of patients is small, these data suggest that the decrease in counts was a consequence of the antiarrhythmic drug treatment.

**Effect of arrhythmia suppression on heart rate variability.** During follow-up study, multiple recordings were obtained in 13 patients in whom despite the same antiarrhythmic treatment (amiodarone in 5, flecainide in 3 and propafenone in 5), no suppression of arrhythmias was observed in one recording, whereas a significant reduction in the number of arrhythmias was observed during a second recording. This group included patients who became responders to a given drug only at the higher dosage and those who were initially responders but became nonresponders despite continuation of treatment at the same dosage, allowing investigation of the specific effect of arrhythmia suppression itself on heart

**Table 2.** Effect of Three Different Antiarrhythmic Drugs on Total 24 h Counts, Heart Rate and Shortening Fraction

	Days on Treatment*	Total 24 h Counts*		Heart Rate (beats/min) <sup>†</sup>		Shortening Fraction (%) <sup>‡</sup>	
		Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
Amiodarone (n = 17)	91 (21-741)	816 (26-13,648)	787 (128-5,449)	78 $\pm$ 12	69 $\pm$ 8‡	21.2 $\pm$ 8	20.6 $\pm$ 6
Flecainide (n = 22)	140 (8-904)	1696 (76-8,643)	680‡ (50-7,834)	75 $\pm$ 11	72 $\pm$ 10	24.2 $\pm$ 9	25.1 $\pm$ 6
Propafenone (n = 17)	188 (11-988)	1637 (132-7,059)	601‡ (10-5,956)	76 $\pm$ 9	76 $\pm$ 8	25.6 $\pm$ 8	26.3 $\pm$ 10

\*Median (range); <sup>†</sup>mean  $\pm$  SD; <sup>‡</sup>significantly different from baseline (see text).

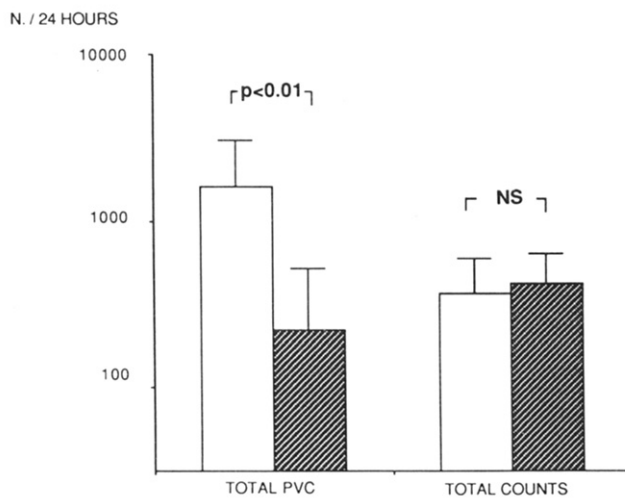
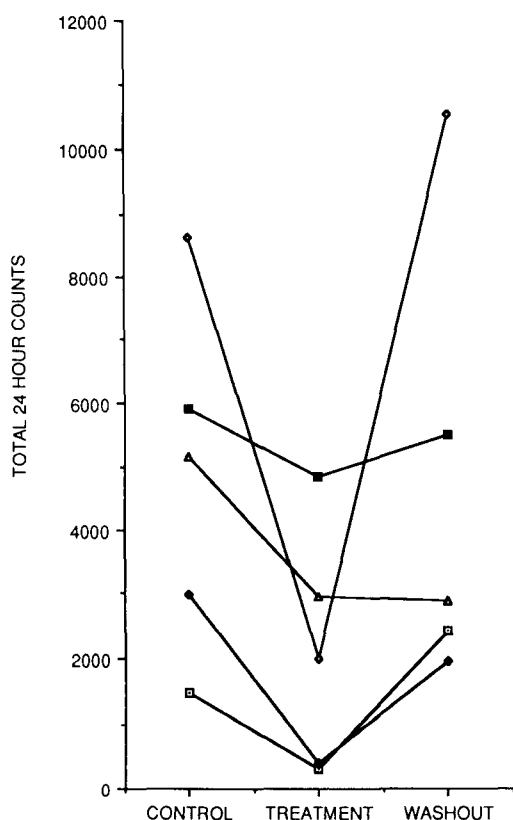


**Figure 4.** Effect of the three antiarrhythmic agents on total 24 h counts in 56 patients with ventricular arrhythmias. Asterisks indicate significant decreases in total 24 h counts from baseline values in patients treated with flecainide and propafenone (see text).

rate variability by comparison of the total 24 h counts in the two recordings.

The mean number of arrhythmias and total 24 h counts are shown in Figure 6. Despite the expected significant difference in the number of arrhythmias in the responder state (median 3.602 premature ventricular complexes/24 h for nonresponders and 320 premature ventricular complexes/24 h for responders,  $p < 0.001$ , Wilcoxon signed rank

**Figure 5.** Individual results from five patients in whom total 24 h counts were measured at baseline (control), during treatment and after drug washout.



**Figure 6.** Effect of suppression of arrhythmias on total 24 h counts in 13 patients with ventricular arrhythmias. Open bars represent group mean values ( $\pm$  standard deviation) when the patients were nonresponders and hatched bars represent values when the same patients were responders. Note that although reduction of isolated premature ventricular complexes (PVC) was not used as a criterion for efficacy in the ADEG study, a major decrease in the number of premature ventricular complexes is apparent in the responder state. However, the number of counts in the two conditions is very similar.

test), the heart rate variability on the two occasions was similar, with a median of 842 counts (range 30 to 5,869) when patients were nonresponders and 640 counts (range 64 to 5,869) when patients were responders, indicating that independent of the drug used, suppression of arrhythmias itself did not affect heart rate variability.

## Discussion

We have shown in this study that our method of measuring heart rate variability, counting the number of successive RR interval differences  $>50$  ms, can be used reliably even in the presence of frequent ventricular ectopic beats. Indeed, the number of such beats does not affect the underlying heart rate variability as measured in this way. The method provides a sensitive indicator of cardiac parasympathetic activity (12,13) and is sufficiently reproducible in individuals with similar clinical conditions to reveal any significant effects caused by different drugs. We therefore observed the effect on cardiac parasympathetic activity of three widely used antiarrhythmic agents and found that flecainide and propafenone each produced a significant and marked reduction in this component of heart rate variability, whereas there was no change with amiodarone.

**Heart rate variability in patients with ventricular arrhythmias.** A number of different techniques have been proposed to assess heart rate variability, both in the time and frequency domain (12,13,26-32). Although it has been suggested that results using time- and frequency-based analyses

are superimposable (33), power spectrum analyses are extremely sensitive to the presence of arrhythmias, need very stable recording conditions and usually cope with only relatively short segments of recording. This may render the frequency domain approach less suitable for 24 h ambulatory monitoring in patients with even small numbers of ventricular ectopic beats. A time-based approach that recently achieved prominence in the analysis of heart rate variability uses the standard deviation around the mean heart rate for different periods (5,6). This method does not measure the same data measured by our counts method because both short- and longer-term variations will be included in the summary standard deviation. Thus, the standard deviation method includes not only purely parasympathetic components, but also sympathetic influences on heart rate variability. Our method has previously been used by us to identify parasympathetic damage in diabetic subjects (12), transplant patients (12) and patients after acute myocardial infarction (13). We recently improved our original method so that it can now handle and exclude even extensive ventricular arrhythmias at 120 times real speed without losing any of the essential heart rate variability data (see Methods).

If meaningful results of the effect of antiarrhythmic agents on heart rate variability are to be obtained, the measured index must be reproducible. We previously showed (12) that our counts method is reproducible in normal and diabetic subjects. The data obtained by comparing two recordings in the same patient, mostly during drug treatment, show that the variability of recordings within the same patient in the present study is relatively small (Fig. 2 and 3), indicating that even in the presence of frequent ventricular arrhythmias, this index of heart rate variability is reliable.

Some baseline count values were at or below the lower end of the normal range. This could be due to the presence of significant cardiac disease in this group of patients. Patients with cardiac failure and ischemic heart disease may have lower heart rate variability than normal subjects (34-36). However, it is unlikely that any alterations in autonomic balance during the acute (13) or subacute (32) phase of myocardial infarction contribute to the low count values because those patients with a previous myocardial infarction were recruited at a stable phase >8 weeks later. Their mean count values did not differ from those of patients with other types of cardiac disease.

#### **Effect of antiarrhythmic agents on heart rate variability.**

Antiarrhythmic drugs theoretically may affect heart rate variability in several ways. The experimental observation (37,38) that the hemodynamic consequence of frequent arrhythmias can alter sympathetic efferent activity at least for brief periods of time suggests that arrhythmias themselves may lead to an imbalance of autonomic discharge to the heart. If this is true, then arrhythmia suppression itself might lead to a change in heart rate variability. However, in this study, two observations did not support this hypothesis. First, there was no correlation between number of counts and number of arrhythmias at baseline study (Fig. 1). Sec-

ond, and perhaps more important, the count rate appeared unaffected when arrhythmias were or were not suppressed by the antiarrhythmic treatment (Fig. 6). This observation suggests that the presence of arrhythmias themselves or their suppression by antiarrhythmic agents does not affect cardiac parasympathetic activity.

*Antiarrhythmic agents may, however, alter heart rate variability by a direct effect on the autonomic nervous system and myocardial contractility.* For example, amiodarone has minimal effects on myocardial performance (14); but in experimental animals, it interacts with the autonomic nervous system at a central (39) and peripheral (40,41) level. Both propafenone and flecainide may reduce myocardial performance (15,16) and may have additional vagolytic (42,43) and beta-blocking (44) properties that might further modulate sympathetic and parasympathetic activity in the heart (14,45). The availability of ambulatory ECG recordings in a homogeneous group of patients during treatment with these three antiarrhythmic drugs has for the first time allowed a comparative analysis of the overall effect of these agents on heart rate variability. Amiodarone did not modify heart rate variability, whereas both flecainide and propafenone reduced it significantly. The return of the count values toward baseline values in most of those patients who were studied after interruption of antiarrhythmic treatment suggests that these changes are reversible. It might be argued that the decrease in heart rate during amiodarone treatment but not during therapy with the other two drugs affected the results. A very strong inverse relation between heart rate and counts would have been required for such a decrease in heart rate to mask a decrease in counts similar to that produced by the other two drugs. We previously showed (12) that the relation between heart rate and counts is complex and variable and by no means strong enough to account for this possibility. Also, we did not find any correlation between drug-induced changes in heart rate and counts.

*Accurate measurements of myocardial contractility were not available in our study patients* because the measured fractional shortening on M-mode echocardiography may not provide a good enough characterization of cardiac function. However, the disparate effect of the three drugs does not appear to be related to major changes in cardiac function, because shortening fraction was not modified during drug treatment, or to a clinical worsening of the patients' condition, because they continued the same treatment when a satisfactory arrhythmia reduction was observed. Class IC antiarrhythmic drugs, perhaps through their negative inotropic properties, might cause sympathetic activation and restore normal cardiac function but still reduce heart rate variability (30) and facilitate the occurrence of malignant arrhythmias (2). Indeed, a link between class IC antiarrhythmic drugs and activation of the sympathetic nervous system was recently suggested (46) by the observation that their proarrhythmic effect may be abolished by the beta-blocking agent propranolol. This sympathetic-parasympathetic imbal-



ance may be undetected by crude indexes (for example, absolute values of heart rate), but may be identified with more subtle indexes of autonomic balance, such as our counts method of measuring heart rate variability.

**Limitations.** Before analyzing the possible implications of these findings, some limitations of this study need to be addressed. This was a retrospective analysis of 24 h ECG recordings from patients enrolled in a clinical trial designed with other end points. Only some of the Antiarrhythmic Drug Evaluation Group (ADEG) study recordings were used for this specific analysis. The reproducibility data were primarily obtained by comparing two recordings measured during drug treatment when the number of arrhythmias was usually lower than at baseline study. Although the results after drug washout are highly suggestive, the small number of patients does not allow any definite conclusion to be drawn on the reversibility of the drug effect on heart rate variability. It is also unclear whether the type of cardiac disease influences the effects of the drugs on heart rate variability.

**Implications of the study.** With these caveats, some tentative conclusions are warranted. Because low values of one measure of heart rate variability (standard deviation) have been associated with an increased mortality rate after myocardial infarction (5,6), a decrease in our count index might also reflect a poor prognosis. The fact that the count rate decreased during treatment with some antiarrhythmic drugs may therefore have important implications. An association between flecainide therapy and an increased mortality rate has already been highlighted in the CAST (11), implying that the sudden deaths may have been due to ventricular tachyarrhythmias and ventricular fibrillation and hence to a proarrhythmic effect of the drug. The late occurrence of these deaths during the course of flecainide therapy is, however, atypical of proarrhythmic drug effects. This was discussed in detail in the consensus statement on the CAST (47), which emphasize that many different mechanisms may be responsible for the deaths and that much remains to be elucidated.

Our new finding that flecainide and propafenone but not amiodarone significantly reduced counts, thus suggesting a decrease in cardiac vagal activity, may improve the understanding of atypical proarrhythmic effects not directly related to the first phase of therapy. The importance of our results to the understanding of the mechanism of action of antiarrhythmic agents and their effect on the incidence of death remains to be clarified. The method, however, offers the prospect of a different approach to the evaluation of antiarrhythmic drugs and, hence, of improving antiarrhythmic therapy.

## Appendix

### Antiarrhythmic Drug Evaluation Group (ADEG)

**Steering Committee:** P. Giani,\* R. Latini,† A. P. Maggioni,‡ P. J. Schwartz,§ G. Tognoni,† A. Volpi,‡

**Coordination and data monitoring:** J. M. Castel, A. Cavalli, V. Giudici, L. Gondoni, M. Landolina, E. Riva, R. Roncoroni, G. Zuanetti.

**Data management and statistical analysis:** F. Colombo, P. Colombo, M. Rocchetti.

**Scientific advisory board:** *Echocardiography:* F. Recusani; *Revision of major clinical events:* A. Selvini; *Endocrinology:* P. Beck Peccoz.<sup>1</sup>

**Participating Clinical Centers:** Aosta (G. Devoti, G. Begliuomini); Casale Monferrato (S. Aletto, D. Corti, M. T. Curti, G. A. Giglio, G. Gozzelino); Como (S. Zerboni); Magenta (G. De Pieri, A. Maggi, M. Mereghetti); Mantova (L. Simeoni); Milano Policlinico (T. Bertoni, A. Finzi, P. Pagnoni); Modena (G. Alfano, F. Melandri, M. C. Tesorieri); Monza (R. Schiavina, F. Valagussa, A. Vincenti); Reggio Emilia (U. Guiducci, A. Manari); Rho (P. Bana, L. Orvieni); Seriate (G. Ferrario, G. Leoni); Sondalo (R. Bigi); Sondrio (G. Cucchi); Torino Ospedale Mauriziano (M. Fazzari); Torino Ospedale Molinette (M. Di Leo, F. Gaita, G. Leone, E. Richiardi); Varese (M. T. Fortunati, M. Luvini); Verona Borgo Trento (E. Barbieri, C. Castello, L. Rossi); Voghera (P. Gandolfi, C. Pasotti).

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\*Ospedale di Seriate, Seriate, Bergamo, Italy; †Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; ‡Ospedale G. Fornaroli, Magenta, Milano, Italy; §Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Milano, Italy; ¶deceased.



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